



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 095 294

A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 83302740.2

(61) Int. Cl.³: C 07 H 19/08
A 61 K 31/70

(22) Date of filing: 16.05.83

(30) Priority: 22.05.82 GB 8215019

(43) Date of publication of application:
30.11.83 Bulletin 83/48

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

(71) Applicant: BEECHAM GROUP PLC
Beecham House Great West Road
Brentford Middlesex(GB)

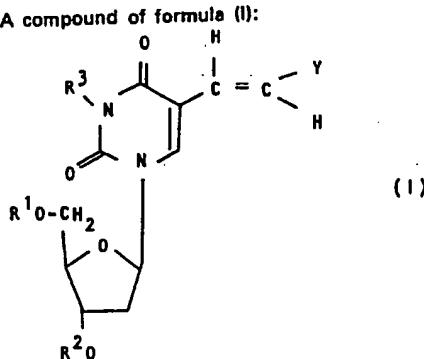
(72) Inventor: Harnden, Michael Raymond
47 Guildford Road
Horsham Sussex(GB)

(72) Inventor: Luk, Kong
4 Palmer Close
Horley Surrey(GB)

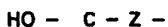
(74) Representative: Russell, Brian John et al,
European Patent Attorney Beecham Pharmaceuticals
Great Burgh Yew Tree Bottom Road
Epsom Surrey, KT18 5XQ(GB)

(54) Deoxyuridine compounds, methods for preparing them and their use in medicine.

(57) A compound of formula (I):



in which X is a C₁₋₁₂ alkyl group an optionally substituted phenyl, or optionally substituted benzyl group, or a carboxy group of the formula



O

in which Z is a branched or straight chain alkylene radical having from 1 to 4 carbon atoms in the chain; an optionally substituted C₁₋₁₂ alkoxy carbonyl group; an optionally substituted C₃₋₁₂ alkenyloxy carbonyl group; an optionally substituted phenoxy carbonyl group; or an optionally substituted phenyl C₁₋₆ alkoxy carbonyl group; provided at least one of R¹, R² and R³ is an optionally substituted alkoxy carbonyl, optionally substituted phenoxy carbonyl or optionally substituted phenyl C₁₋₆ alkoxy carbonyl group, is useful in treating virus infections.

or a pharmaceutically acceptable salt or ester thereof, in which Y is a hydrogen or halogen atom, preferably a bromine atom, and each of R¹, R² and R³ is a hydrogen atom; an acyl radical of the formula



O

EP 0 095 294 A1

-1-

0095294

DEOXYURIDINE COMPOUNDS, METHODS FOR PREPARING THEM AND
THEIR USE IN MEDICINE

This invention relates to certain deoxyuridine compounds which have antiviral activity.

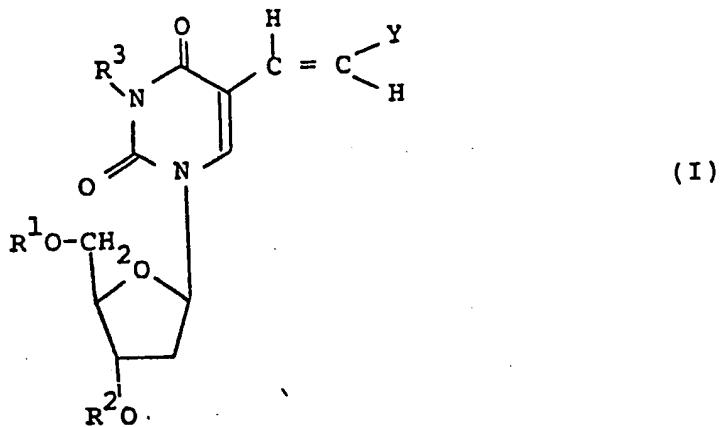
Published European Patent Application No. 0 061 283 discloses esters of 5-(2-halogenovinyl)-2'-deoxyuridines which have antiviral activity selective against herpes viruses.

We have now found a group of mono-, di- and tri-substituted 5-(2-halogenovinyl)-2'-deoxyuridines which have excellent antiviral activity, and which are especially useful in the treatment of infections caused by herpes viruses, such as herpes simplex type 1, herpes simplex type 2 and varicella.

- 2 -

0095294

According to the present invention there is provided a compound of formula (I):



or a pharmaceutically acceptable salt or ester thereof,

in which Y is a hydrogen or halogen atom, and each of R¹, R² and R³ is a hydrogen atom; an acyl radical of the formula X - C = O, in

which X is a C₁-12 alkyl group, an optionally substituted phenyl, or optionally substituted benzyl group, or a carboxy group of the formula HO - C = O - Z -

in which

Z is a branched or straight chain alkylene radical having from 1 to 4 carbon atoms in the chain; an optionally substituted C₁-12 alkoxy carbonyl group; an optionally substituted C₃-12 alkenyloxy carbonyl group; an optionally substituted phenoxy carbonyl group; or an optionally substituted phenyl C₁-6 alkoxy carbonyl group; provided at least one of R¹, R² and R³ is an

- 3 -

0095294

optionally substituted alkoxy carbonyl, optionally substituted alkenyloxy carbonyl, optionally substituted phenoxy carbonyl or optionally substituted phenyl C₁₋₆ alkoxy carbonyl group.

Preferably, Y is a bromine atom

The C₁₋₁₂ alkoxy moiety may be branched or unbranched.

Preferred alkoxy carbonyl groups are C₁₋₆ alkoxy carbonyl groups, suitably methoxycarbonyl and ethoxycarbonyl.

When the alkoxy moiety contains two or more carbon atoms, the moiety may be optionally substituted by hydroxyl on any carbon atom not adjacent to the oxygen atom.

Preferred alkenyloxy carbonyl groups are C₃₋₆ alkenyloxy carbonyl groups such as propenyl.

Preferred phenoxy carbonyl groups are those wherein the optional substituents may be one or more stable moieties, such as halogen, nitro, alkoxy or alkyl.

Preferred phenyl C₁₋₆ alkoxy carbonyl groups are optionally substituted benzyloxy carbonyl groups, wherein the optional substituents may be one or more stable moieties as mentioned above.

Preferred acyl radicals are those wherein X is C₁₋₆ alkyl or Z is (-CH₂-)_n wherein n is 2 or 3.

- 4 -

0095294

Preferred esters are those wherein one of R¹ or R² is a phosphate group and the other is optionally substituted alkoxy carbonyl, optionally substituted alkenyloxy carbonyl, optionally substituted phenoxy carbonyl or optionally substituted phenyl C₁-6 alkoxy carbonyl. Particularly preferred esters are those wherein R² is a phosphate group.

Preferred salts of the compounds of formula (I) are alkali metal salts of the HO - $\begin{array}{c} \text{C} \\ || \\ \text{O} \end{array}$ - Z moiety,

or alkali metal salts of the phosphate esters.

Particularly preferred compounds are those wherein R¹ or R² is an optionally substituted alkoxy carbonyl, optionally substituted alkenyloxy carbonyl, optionally substituted phenoxy carboxyl or optionally substituted phenyl C₁-6 alkoxy carboxyl group.

Examples of compounds of the invention are as follows:

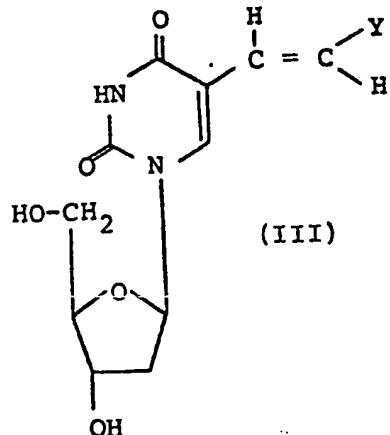
5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-methoxy-carbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3'-O-methoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-methoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-ethoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3'-O-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3,3'-O-bisvaleryluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3'-O-valeryluridine;

0095294

5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3-valeryluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine 3'-Succinate Sodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine 3'-Phosphate Disodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine 3'-Phosphate Monosodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-propoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-5'-O-n-butoxycarbonyl-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-3',5'-bis-O-butoxycarbonyl-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-5'-O-isobutoxycarbonyl-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-5'-O-t-butoxycarbonyl-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-3',5'-bis-O-t-butoxycarbonyl-2'-deoxyuridine;
5-(E-2-Bromovinyl)-3'-O-t-butoxycarbonyl-2'-deoxy-uridine;
5'-O-Allyloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxy-uridine;
5'-O-Benzylloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-5'-O-phenoxy carbonyl-2'-deoxy-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(p-nitrophenoxy-carbonyl)uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-isopropoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(2-hydroxyethoxy-carbonyl)uridine;
2'-Deoxy-5'-O-ethoxycarbonyl-5-vinyluridine;

0095294

Compounds of formula (I) wherein R¹ or R² is optionally substituted C₁₋₁₂ alkoxy carbonyl, optionally substituted C₃₋₁₂ alkenyloxy carbonyl, optionally substituted phenoxy carbonyl or optionally substituted phenyl C₁₋₆ alkoxy carbonyl, and R³ is a hydrogen atom, may be prepared by reacting a compound of formula (III):



in which Y is as defined in formula (I), with the appropriate alkyl, alkenyl, phenyl or phenylalkyl chloroformate.

The reaction is suitably carried out in an anhydrous organic solvent in the presence of a base, preferably at depressed or room temperature, and the product purified chromatographically by, for example, column chromatography on silica gel.

Examples of suitable solvent systems for carrying out the reaction are anhydrous pyridine, tetrahydrofuran/sodium carbonate, and tetrahydrofuran/triethylamine.

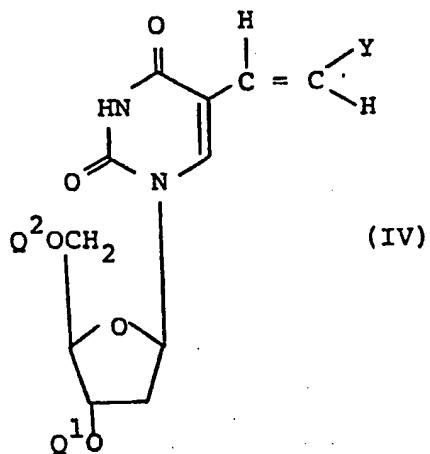
The reaction will generally produce a mixture of products wherein both of R¹ and R² are alkoxy-, alkenyloxy-, phenoxy- or phenylalkoxy-carbonyl groups, and each of R¹ and R² is a hydrogen atom while the

- 7 -

0095294

other is alkoxy-, alkenyloxy-, phenoxy- or phenylalkoxy-carbonyl. The mixture can be separated into its pure components by chromatographic methods. The relative amounts of products will depend on the relative amounts of reactants, the physical conditions of the reaction, and the solvent system. For example, an excess of chloroformate will produce more of the disubstituted compound in the final mixture.

Compounds of formula (I) wherein R³ is alkoxy-, alkenyloxy-, phenoxy- or phenylalkoxy-carbonyl as defined above, and R¹ and R² are each hydrogen atoms, may be prepared by treating a compound of formula (IV):



wherein Y is as defined in formula (I), and Q¹ and Q² are O-protecting groups, with the appropriate alkyl, alkenyl, phenyl- or phenylalkyl-chloroformate, and deprotecting the resultant product.

Suitable O-protecting groups are trialkylsilyl groups, such as trimethylsilyl.

0095294

The reaction is suitably carried out in an anhydrous organic solvent in the presence of a base, preferably at room temperature, and the product may be purified by column chromatography on silica gel.

The compound of formula (IV) may be prepared by treating a compound of formula (III) as defined above, with a silylating agent.

Suitable silylating agents include halosilanes or silazanes of the formulae:

$L_3 Si U$; $L_3 Si NL_2$;
 $L_3 Si NH Si L_3$; $L_3 Si.NH.COL$; $L_3 Si.NH.CO.NH.Si L_3$;
 $L.NH.CO.NH.Si L_3$; $L_3 Si N = CLO Si L_3$.

wherein U is a halogen and the various groups L which may be the same or different, each represents hydrogen or alkyl, aryl or aralkyl.

A preferred silylating agent is N,O-bistrimethyl-silylacetamide, and the silylation reaction is preferably carried out in an anhydrous organic solvent, suitably tetrahydrofuran, at room temperature.

The product may be purified chromatographically by, for example, column chromatography on silica gel.

The protected compound of formula (IV), wherein Q¹ is replaced by a hydrogen atom, may also be used to prepare compounds of formula (I), wherein R² is alkoxy-, alkenyloxy-, phenoxy- or phenylalkoxy-carbonyl and R¹ and R³ are each hydrogen atoms, by treatment with an alkyl-, alkenyl-, phenyl- or phenylalkyl-chloroformate and deprotecting the resultant product. The reaction conditions are similar to those described above.

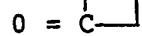
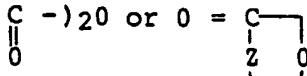
0095294

Compounds of formula (I) wherein R¹, R² or R³ is an acyl group as defined, may be prepared by treating the compounds of formula (I) wherein R¹, R² or R³ is a hydrogen atom, with an acylating agent containing the X - C - group or - Z - C - group, wherein



X and Z are as defined with respect to formula (I).

A preferred acylating agent is an acid anhydride of formula (X - C -)₂O or O = C -



or an acid chloride of formula X - C - Cl



The reaction is conveniently carried out in an anhydrous organic solvent such as tetrahydrofuran in the presence of a base or pyridine, and the product purified by column chromatography on silica gel.

In the case where, in the reactant of formula (I), R¹ is alkoxy-, alkenyloxy-, phenoxy- or phenylalkoxy-carbonyl, and R² and R³ are both hydrogen atoms, the reaction will generally produce a mixture of three products, wherein each one of the two hydrogen atoms is replaced by an acyl group while the other hydrogen atom remain intact, and wherein both hydrogen atoms are replaced by acyl groups.

The mixture can be separated into its pure components by chromatographic methods. In order to prepare compounds of formula (I) wherein two of R¹, R² and R³ are different acyl groups, the mono-acylated compounds prepared as described above may be isolated from the three product mixture and further treated with a different acylating agent under similar reaction conditions. In this way, any combination of acylated derivatives may be prepared, as required.

Q095294

Certain compounds of formula (I) can themselves be converted to other compounds of formula (I).

For example, compounds of formula (I) in which R¹ is optionally substituted phenoxy carbonyl may be converted into compounds wherein R¹ is C₁-12 alkoxy carbonyl by treatment with a C₁-12 alkanol, preferably in the presence of a basic organic solvent such as pyridine. In a similar manner, treatment with a C₂-12 diol, in place of the C₁-12 alkanol, will yield a compound of formula (I) wherein R¹ is hydroxy substituted C₂-12 alkoxy carbonyl.

Phosphate esters of the compounds of formula (I) may be prepared by treating a compound of formula (I), in which R¹ or R² is hydrogen, with phosphoryl chloride, preferably in an anhydrous basic organic solvent such as pyridine. The ester can be suitably prepared in the form of an alkali metal salt by the addition of an alkali metal bicarbonate to the ester.

The compounds of formula (I) or salts or esters thereof may be formulated for use in a pharmaceutical composition. Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier or excipient.

Compositions which may be administered by the oral route to humans may be compounded in the form of syrups, tablets and capsules. When the composition is in the form of a tablet, any pharmaceutical carrier suitable for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose,

0095294

glucose, rice, flour and chalk. The composition may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups. The compounds may also be presented with a sterile liquid carrier for injection.

The composition may also be formulated for topical application to the skin or eyes.

For topical application to the skin, the compounds of the invention may be made up into a cream, lotion or ointment. These formulations may be conventional formulations well known in the art, for example, as described in standard books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books and the British Pharmacopoeia.

The composition for application to the eyes may be a conventional eye-drop composition well known in the art.

Preferably, the compositions of this invention are in unit dosage form or in some other form that the patient may administer to himself a single dose. A suitable dosage unit might contain from 50 mg to 1 g of active ingredient, for example 100 to 500 mg. Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound depends on the particular compound employed, but is in general in the range of from 1.0 to 20 mg/kg of body weight per day or more usually 2.0 to 10 mg/kg per day.

- 12 -

0095294

In a further aspect of the invention there is provided a method of treating viral infections in human and non-human animals, which comprises administering to the sufferer an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof.

The following Examples illustrate the invention.

Examples 1, 2 and 3**0095294**

5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-methoxycarbonyluridine (Example 1), 5-(E-2-Bromovinyl)-2'-deoxy-3'-O-methoxycarbonyluridine (Example 2) and 5-(E-2-Bromovinyl)-2'-deoxy-5'-O-methoxycarbonyluridine (Example 3)

5

10

15

20

25

30

35

Methyl chloroformate (2ml) was added to a stirred mixture of 5-(E-2-bromovinyl)-2'-deoxyuridine (1.05g) and anhydrous sodium carbonate (1.5g) in dry tetrahydrofuran (30ml) at -30°. The mixture was allowed to come to room temperature and stirred at room temperature for 18 h. It was then partitioned between ethyl acetate and water. The organic extract was dried and evaporated and the residue was chromatographed over silica gel (40g). Elution with ethyl acetate-hexane (4:1) gave 5-(E-2-bromovinyl)-2'-deoxy-3',5'-bis-O-methoxycarbonyluridine (0.09g), m.p. 170-178° (from ethyl acetate-hexane), λ_{max} (EtOH) 249 (ϵ 13,200) and 292 (ϵ 11,100) nm; ν_{max} (KBr) 1760, 1745, 1690, and 1270 cm^{-1} ; δ_{H} [(CD₃)₂SO] 2.50 (2H, m, 2'-CH₂), 3.74 (6H, s, OCH₃), 4.20 (1H, m, 4'-CH), 4.34 (2H, m, 5'-CH₂), 5.18 (1H, m, 3'-CH), 6.16 (1H, broad t, J 6Hz, 1'-CH), 6.85 (1H, d, J 14Hz, CH=CHBr), 7.29 (1H, d, J 14Hz, CH=CHBr), 7.84 (1H, s, 6-CH), and 11.64 (1H, broad s, D₂O exchangeable, NH) (Found: C, 40.3; H, 3.50; N, 6.0 %. C₁₅H₁₇N₂O₉Br requires C, 40.1; H, 3.8; N, 6.25 %); 5-(E-2-bromovinyl)-2'-deoxy-3'-O-methoxycarbonyluridine (0.17g), λ_{max} (EtOH) 249 (ϵ 13,900) and 292 (ϵ 11,700) nm; ν_{max} (CHCl₃) 1750, 1710, and 1280 cm^{-1} ; δ_{H} (CDCl₃) 2.51 (2H, m, 2'-CH₂), 2.70 (1H, m, D₂O exchangeable, OH), 3.84 (3H, s, OCH₃), 3.96 (2H, m, 5'-CH₂), 4.23 (1H, m, 4'-CH), 5.30 (1H, m, 3'-CH), 6.27 (1H, t, J 6Hz, 1'-CH), 6.66 (1H, d, J 14Hz, CH=CHBr), 7.35 (1H, d, J 14Hz, CH=CHBr), 7.87 (1H, s, 6-CH), and 9.22 (1H, broad s, D₂O exchangeable, NH) (Found: C, 40.2; H, 3.75; N, 6.6 %. C₁₃H₁₅N₂O₇Br requires C, 39.9; H, 3.85; N, 7.15 %); and 5-(E-2-bromovinyl)-2'-deoxy-5'-O-methoxycarbonyluridine (0.1g), m.p. 185-186° (from acetone-hexane), λ_{max} (EtOH) 249 (ϵ 13,800) and 292 (ϵ 11,700) nm; ν_{max} (KBr) 1758, 1742,

- 14 -

0095294

1710, 1690, 1678, 1390, 1365, and 1082 cm^{-1} ; $\delta_{\text{H}}^{1}\text{H}[(\text{CD}_3)_2\text{SO}]$
2.22 (2H, t, J 6Hz, 2'- CH_2), 3.72 (3H, s, OCH_3), 3.83-
4.40 (4H, m), 5.42 (1H, m, D_2O exchangeable, OH), 6.16
(1H, t, J 6Hz, 1'- CH), 6.87 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$),
7.30 (1H, d, J 6Hz, $\text{CH}=\text{CHBr}$), 7.80 (1H, s, 6- CH), and
11.58 (1H, m, D_2O exchangeable, NH) (Found: C, 40.1;
H, 3.75; N, 7.1 %, M+ 390. $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_7\text{Br}$ requires
C, 39.9; H, 3.85; N, 7.15 % M+ 390).

5

Example 4**0095294**5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-ethoxycarbonyl-uridine

Ethyl chloroformate (2.5ml) was added slowly to a stirred mixture of 5-(E-2-bromovinyl)-2'-deoxuridine (2.2g) and 4-dimethylaminopyridine (0.2g) in pyridine (30ml) at 0°. The mixture was then stirred at room temperature overnight. It was then poured into water and extracted with ethyl acetate. The organic extract was washed with aqueous hydrochloric acid, brine, aqueous sodium bicarbonate, dried, and evaporated. The residue was chromatographed over silica gel (80g). Elution of the column with ethyl acetate-hexane (1:1) gave the title compound (1.6g), m.p. 148-152° (from hexane=ethyl acetate), λ_{max} (EtOH) 249 (ϵ 14,900) and 293 (ε 12,400) nm; ν_{max} (KBr) 1750, 1712, 1682, and 1270 cm^{-1} ; δ_H [(CD₃)₂SO] 1.24 (6H, t, J 7.2Hz, -OCH₂CH₃), 2.45 (2H, m, 2'-CH₂), 4.15 (4H, q, J 7.2Hz, -OCH₂CH₃), 4.33 (3H, m, 4'-CH, 5'-CH₂), 5.19 (1H, m, 3'-CH), 6.16 (1H, t, J 6.8Hz, 1'-CH), 6.84 (1H, d, J 13.7Hz, CH=CHBr), 7.30 (1H, d, J 13.7Hz, CH=CHBr), 7.84 (1H, s, 6-CH), and 11.62 (1H, m, D₂O exchangeable, NH) (Found: C, 42.8; H, 4.3; N, 5.65 %. C₁₇H₂₁N₂O₉Br requires C, 42.8; H, 4.45; N, 5.85 %).

- 16 -

Example 5

0095294

5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine

Ethyl chloroformate (1.5ml) was added slowly over 0.5 h to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (5g) in pyridine (100ml) at 0° and the mixture was stirred at room temperature for 1 h. It was then partitioned between ethyl acetate and water. The organic extract was dried and evaporated, affording a colourless solid which was chromatographed over silica gel (150g). Elution with hexane-ethyl acetate (1:4) gave the title compound (2.5g), m.p. 198-204°, λ_{max} (EtOH) 293 (ϵ 12,400) and 249 (ϵ 14,700) nm; ν_{max} (KBr) 1748, 1715, 1695, 1672, 1288, 1255, and 1078 cm^{-1} ; δ_H [(CD₃)₂SO] 1.23 (3H, t, J 7.5Hz, OCH₂CH₃), 2.20 (2H, broad t, J 6Hz, 2'-CH), 3.90-4.33 (6H, m), 5.45 (1H, D₂O exchangeable, OH), 6.19 (1H, t, J 6Hz, 1'-CH), 6.90 (1H, d, J 14Hz, CH=CHBr), 7.35 (1H, d, J 14Hz, CH=CHBr), 7.83 (1H, s, 6-CH), and 11.7 (1H, broad s, NH) (Found: C, 41.6; H, 4.25; N, 6.8 %, M⁺ 404. C₁₄H₁₇N₂O₇Br requires C, 41.5; H, 4.25; N, 6.9 %, M⁺ 404).

Example 6

0095294

5-(E-2-Bromovinyl)-2'-deoxy-3'-O-ethoxycarbonyluridine

Ethyl chloroformate (0.5ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)uridine (1.4g) in pyridine (20ml) at 0°. The mixture was then stirred at room temperature for 1 h. It was then partitioned between ethyl acetate and water. The organic extract was dried and evaporated, affording an oil which was chromatographed over silica gel (60g). Elution with ethyl acetate-hexane (1:1) gave 5-(E-2-bromovinyl)-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)-3'-O-ethoxycarbonyluridine (0.85g), λ_{max} (EtOH) 235 (ϵ 29,400) and 283 (ϵ 11,700) nm; ν_{max} (CHCl₃) 1720, 1690, and 1255 cm⁻¹; δ_{H} (CDCl₃) 1.30 (3H, t, J 7.5Hz, OCH₂CH₃), 2.23-2.80 (2H, m, 2'-CH₂), 3.48 (2H, m, 5'-CH₂), 4.22 (2H, q, J 7.5Hz, OCH₂CH₃), 4.26 (1H, m, 4'-CH), 5.38 (1H, m, 3'-CH), 5.81 (1H, d, J 14Hz, CH=CHBr), 6.43 (1H, m, 1'-CH), 6.89 (4H, d, J 9Hz, ArH), 7.20-7.44 (10H, m, ArH, CH=CHBr), 7.73 (1H, s, 6-CH), and 8.86 (1H, broad s, D₂O exchangeable, NH) (Found: C, 59.1; H, 4.75; N, 3.9 %. C₃₅H₃₅N₂O₉Br requires C, 59.40; H, 5.0; N, 3.95 %).

A solution of the 5-(E-2-bromovinyl)-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)-3'-O-ethoxycarbonyluridine in 80% aqueous acetic acid (20ml) was stirred at room temperature for 0.75 h. The mixture was then partitioned between ethyl acetate and water. The organic extract was washed with water, bicarbonate, brine, dried and evaporated. The residue was chromatographed over silica gel (30g). Elution of the column with ethyl acetate-hexane (3:2) gave the title compound (0.36g), λ_{max} 249 (ϵ 14,000) and 292 (ϵ 11,800) nm; ν_{max} (CHCl₃) 1710 (broad) and 1270 cm⁻¹; δ_{H} (CDCl₃) 1.32 (3H, t, J 7.5Hz, OCH₂CH₃), 2.47 (2H, m, 2'-CH₂), 2.82 (1H, m, D₂O exchangeable, OH), 3.97 (2H, m, 5'-CH₂), 4.22 (2H, q, J 7.5Hz, OCH₂CH₃), 4.25 (1H, m, 4'-CH), 5.29 (1H, m, 3'-CH), 6.29 (1H, broad t, J 6Hz, 1'-CH), 6.66 (1H, d, J 14Hz, CH=CHBr), 7.36 (1H, d, J 14Hz, CH=CHBr), 7.91 (1H, s, 6-CH), and 9.45 (1H, m, D₂O exchangeable, NH)

- 18 -

(Found: C, 41.85; H, 4.0; N, 6.5 %. C₁₄H₁₇N₂ 0095294
requires C, 41.5; H, 4.25; N, 6.9 %).

Example 7**0095294**5-(E-2-Bromovinyl)-2'-deoxy-3-ethoxycarbonyluridine

To a stirred solution of 3',5'-bis-O-trimethylsilyl-5-(E-2-bromovinyl)-2'-deoxyuridine (0.6g) in tetrahydrofuran (15ml), 4-dimethylaminopyridine (0.01g) and triethylamine (0.5ml) were added followed by ethyl chloroformate (0.2ml). The mixture was stirred at room temperature for 2 h. Further ethyl chloroformate (0.2ml) was then added and the mixture stirred at room temperature for another 2 h. It was then partitioned between ethyl acetate and water. The organic extract was dried and evaporated, affording an oil which was chromatographed over silica gel (20g). Elution of the column with n-hexane-ethyl acetate (1:4) gave the title compound, m.p. 136-140° (ethyl acetate-hexane), λ_{max} (EtOH) 250 (ϵ 14,300) and 297 (ϵ 11,200) nm; ν_{max} (KBr) 1794, 1732, 1660, 1460, 1282, and 1232 cm^{-1} ; δ_{H} [(CD₃)₂SO] 1.30 (3H, t, J 7.5Hz, OCH₂CH₃), 2.22 (2H, m, 2'-CH₂), 3.62 (2H, m, 5'-CH₂), 3.83 (1H, m, 4'-CH), 4.25 (1H, m, 3'-CH), 4.42 (1H, q, J 7.5Hz, OCH₂CH₃), 5.03-5.20 (2H, m, OH), 6.10 (1H, t, J 6Hz, 1'-CH), 6.87 (1H, s, J 14Hz, CH=CHBr), 7.23 (1H, d, J 14Hz, CH=CHBr), and 8.23 (1H, s, 6-CH) (Found: C, 41.0; H, 4.35; N, 6.85 %, M⁺ 404. C₁₄H₁₇N₂O₇Br requires C, 41.5; H, 4.25; N, 6.9 %, M⁺ 404).

- 20 -

Examples 8, 9 and 10**0095294**

5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3,3'-O-bisvaleryluridine (Example 8), 5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3'-O-valeryluridine (Example 9) and 5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3-valeryluridine (Example 10)

To a stirred solution of 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine (0.46g) in tetrahydrofuran (20ml) at 0°, triethylamine (0.24ml) was added followed by valeryl chloride (0.15ml) and the mixture was stirred at 0° for 0.5 h. A further portion of triethylamine (0.24ml) and valeryl chloride (0.15ml) was added and the mixture stirred for another 0.5 h at 0°. It was then partitioned between ethyl acetate and water. The organic extract was dried and evaporated, affording an oil which was chromatographed over silica gel (20g). Elution with n-hexane-ethyl acetate gave 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3,3'-O-bisvaleryluridine (0.12g), ν_{max} (CHCl₃) 1790, 1750, 1730, 1710, 1670, and 1260 cm⁻¹; δ_{H} (CDCl₃) 0.93 (6H, t, J 7Hz), 1.40 (3H, t, J 7.5Hz, OCH₂CH₃), 1.14-1.90 (8H, m), 2.10-2.62 (4H, m), 2.60 (2H, t, J 7.5Hz), 4.15-4.47 (5H, m), 5.24 (1H, m, 3'-CH), 6.37 (1H, m, 1'-CH), 6.69 (1H, d, J 14Hz, CH=CHBr), 7.38 (1H, d, J 14Hz, CH=CHBr), and 7.73 (1H, s, CH=CHBr); and 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-6-CH); and 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3'-O-valeryluridine (0.05g), ν_{max} (CHCl₃) 1750, 1710, and 1260 cm⁻¹; δ_{H} (CDCl₃) 0.90 (3H, t, J 7Hz), 1.35 (3H, t, J 7.5Hz, OCH₂CH₃), 1.14-1.74 (4H, m), 2.02-2.60 (4H, m), 4.13-4.60 (5H, m), 5.30 (1H, m, 3'-CH), 6.40 (1H, m, 1'-CH), 6.67 (1H, d, J 14Hz, CH=CHBr), 7.40 (1H, d, J 14Hz, CH=CHBr), 7.70 (1H, s, 6-CH), and 9.57 (1H, m, D₂O exchangeable, NH); followed by 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3-valeryluridine (0.25g), ν_{max} (CHCl₃) 1790, 1750, 1710, 1360, and 1290 cm⁻¹; δ_{H} (CDCl₃) 0.89 (3H, t, J 7Hz), 1.34 (3H, t, J 7.5Hz, OCH₂CH₃), 1.10-1.84 (4H, m), 1.97-2.55 (2H, m, 2'-CH₂), 2.77 (2H, t, J 7.5Hz), 3.34 (1H, m, D₂O exchangeable, OH), 4.05-4.50 (6H, m), 6.28 (1H, t, J 6Hz, 1'-CH), 6.70 (1H, d, J 14Hz, CH=CHBr), 7.36 (1H, d, J 14Hz, CH=CHBr), and 7.76 (1H, s, 6-CH).

Example 11**0095294**5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine
3'-Succinate Sodium Salt

A mixture of 5-(E-2-bromovinyl)-2'-deoxy-5'-O-ethoxy-carbonyluridine (0.11g), 4-dimethylaminopyridine (0.1g), and succinic anhydride (0.05g) in pyridine (2ml) was stirred at room temperature for 70 h. It was then evaporated to dryness. The residue was partitioned between aqueous hydrochloric acid and ethyl acetate. The organic layer was washed with water and then extracted with water at pH 7.5. The aqueous extract was concentrated to 4ml and filtered through 2 C₁₈ Sep-Pak cartridges, elution with aqueous methanol gave the title compound (0.09g), λ_{max} (H₂O) 249 (ϵ 14,400) and 293 (ϵ 10,900) nm; ν_{max} (KBr) 1740, 1710, 1690, 1585, 1285, and 1260 cm⁻¹; δ_H (D₂O) 1.20 (3H, t, J 7.5Hz, 2'-CH₂), 2.10-2.73 (6H, m), 4.00-4.43 (5H, m), 5.23 (1H, m, 3'-CH), 6.20 (1H, m, 1'-CH), 6.54 (1H, d, J 14Hz, CH=CHBr), 7.10 (1H, d, J 14Hz, CH=CHBr), and 7.60 (1H, s, 6-CH).

0095294

Example 125-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine
3'-Phosphate Disodium Salt

5 Phosphoryl chloride (0.03ml) in pyridine (1ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxy-
5'-O-ethoxycarbonyluridine (0.11g) in pyridine (2ml) at
room temperature and the mixture was stirred at room
temperature for 0.5 h. It was evaporated to dryness and
the residue dissolved in water (10ml). Sodium bicarbonate
10 (0.125g) was then added and the solution was evaporated to
dryness. The residue was filtered through 2 C₁₈ Sep-Pak
cartridges. Elution with aqueous methanol gave the title
compound (0.05g), ν_{max} (KBr) 1745, 1710, 1690, 1285, 1260,
1085, 1010, and 945 cm⁻¹; δ_{H} [(CD₃)₂SO] 1.22 (3H, t,
15 J 7.5Hz, OCH₂CH₃), 2.38 (2H, m, 2'-CH₂), 3.96-4.55 (5H, m,
5'-CH₂, 4'-CH, OCH₂CH₃), 4.83 (1H, m, 3'-CH), 6.20 (1H, m,
1'-CH), 6.85 (1H, d, J 14Hz, CH=CHBr), 7.31 (2H, d, J 14Hz,
CH=CHBr), 7.88 (1H, s, 6-CH), and 11.60 (1H, m, D₂O
exchangeable, NH).

Example 13**0095294**5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine
3'-Phosphate Monosodium Salt

Phosphoryl chloride (0.03ml) in pyridine (1ml) was
5 added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxy-
5'-O-ethoxycarbonyluridine (0.11g) in pyridine (2ml) at
room temperature and the mixture was stirred at room
temperature for 0.5 h. It was evaporated to dryness and
10 the residue dissolved in water (10ml). Sodium bicarbonate
(0.1g) was then added and the solution was evaporated to
dryness. The residue was filtered through 2 C₁₈ Sep-Pak
cartridges. Elution with aqueous methanol gave the title
compound (0.04g), δ_H (D₂O) 1.20 (3H, t, J 7.5Hz, OCH₂CH₃),
2.40 (2H, m, 2'-CH₂), 4.00-4.53 (5H, m, 5'-CH₂, 4'-CH,
15 OCH₂CH₃), 4.73 (1H, m, 3'-CH), 6.20 (1H, t, J 6.5Hz, 1'-CH),
6.63 (1H, d, J 14Hz, CH=CHBr), 7.08 (1H, d, J 14Hz, CH=CHBr),
and 7.65 (1H, s, 6-CH).

Example 14**0095294**5-(E-2-Bromovinyl)-2'-deoxy-5'-O-propoxycarbonyluridine

Propyl chloroformate (0.5ml) was added to a solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (1.22g) in pyridine (20ml) at 0° and the mixture was stirred at 0° for 1 h.

5 It was then partitioned between water and ethyl acetate. The organic extract was washed with aqueous hydrochloric acid, brine, sodium bicarbonate, dried, and evaporated. The residue was chromatographed over silica gel (60g).

10 Elution of the column with ethyl acetate-hexane (9:1) gave the title compound (1.0g), m.p. 171-173° (from ethyl acetate-ether), λ_{max} (EtOH) 249 (ϵ 14,400) and 293 (ϵ 12,400) nm; ν_{max} (KBr) 1750, 1710, 1690, 1675, 1470, and 1282 cm^{-1} ; δ_{H} [(CD₃)₂SO] 0.90 (3H, t, J 7.5Hz), 1.63 (2H, m), 2.30 (2H, t, J 6Hz, 2'-CH₂), 3.83-4.40 (6H, m), 5.40 (1H, m, D₂O exchangeable, CH), 6.34 (1H, t, J 6Hz, 1'-CH), 6.83 (1H, d, J 14Hz, CH=CHBr), 7.28 (1H, d, J 14Hz, CH=CHBr), 7.77 (1H, s, 6-CH), and 11.55 (1H, m, D₂O exchangeable, NH) (Found: C, 43.2; H, 4.45; N, 6.5 %. C₁₅H₁₉N₂O₇Br requires C, 42.95; H, 4.55; N, 6.7 %).

- 25 -

0095294

Example 15

5-(E-2-Bromovinyl)-5'-O-n-butoxycarbonyl-2'-deoxyuridine

n-Butyl chloroformate (0.7g) was added to a solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (1.43g) in pyridine (25ml) at 0° and the mixture was stirred at room temperature for 1 h. The same work-up and chromatography as in Example 14 gave the title compound (1.2g), m.p. 150-153° (from ethyl acetate-hexane), λ_{max} (EtOH) 249 (ϵ 12,900) and 293 (ϵ 11,200) nm; ν_{max} (KBr) 1750, 1715, 1685, 1275, and 1160 cm^{-1} ; δ_H [(CD₃)₂SO] 0.87 (3H, t, J 7.5Hz), 1.10-1.76 (4H, m), 2.17 (2H, t, J 6.5Hz, 2'-CH₂), 3.80-4.40 (6H, m), 5.40 (1H, m, D₂O exchangeable, OH), 6.33 (1H, t, J 6.5Hz, 1'-CH), 6.82 (1H, d, J 14Hz, CH=CHBr), 7.27 (1H, d, J 14Hz, CH=CHBr), 7.75 (1H, s, 6-CH), and 11.56 (1H, m, D₂O exchangeable, NH) (Found: C, 44.8; H, 5.0; N, 6.4 %. C₁₆H₂₁N₂O₇Br requires C, 44.35; H, 4.9; N, 6.45%).

Examples 16 and 17

0095294

5-(E-2-Bromovinyl)-3',5'-bis-O-isobutoxycarbonyl-2'-deoxyuridine (Example 16) and 5-(E-2-Bromovinyl)-5'-O-isobutoxycarbonyl-2'-deoxyuridine (Example 17)

5 isoButyl chloroformate (1.6ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (2.05g) in pyridine (30ml) at 0° and the mixture was stirred at room temperature for 1 h. It was then partitioned between aqueous hydrochloric acid (5M) and ethyl acetate. The organic layer was washed with brine, aqueous sodium bicarbonate, dried, and evaporated. The residue was chromatographed over silica gel (80g). Elution of the column with ethyl acetate-hexane (4:1) afforded 5-(E-2-bromovinyl)-3',5'-bis-O-isobutoxycarbonyl-2'-deoxyuridine (1.36g), m.p. 100-101° (from ether-hexane), λ_{max} (EtOH) 249 (ϵ 14,500) and 292 (ϵ 12,400) nm; ν_{max} (KBr) 1750, 1705, and 1250 cm^{-1} ; δ_{H} (CDCl_3) 1.00 (12H, d, J 7Hz, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.83-2.75 (4H, m, 2'-CH, $-\text{CH}_2\text{CHMe}_2$), 3.95 (2H, d, J 7Hz, $-\text{CH}_2\text{CHMe}_2$), 4.05 (2H, d, J 7Hz, $-\text{CH}_2\text{CHMe}_2$), 4.36 (1H, m, 4'-CH), 4.45 (2H, m, 5'- CH_2), 5.20 (1H, m, 3'-CH), 6.42 (1H, m, 1'-CH), 6.67 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.45 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.67 (1H, s, 6-CH), and 9.06 (1H, m, D_2O exchangeable, NH) (Found: C, 47.55; H, 5.4; N, 5.2%). $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_9\text{Br}$ requires, C, 47.3; H, 5.5; N, 5.25%), followed by 5-(E-2-bromovinyl)-5'-O-isobutoxycarbonyl-2'-deoxyuridine (1.37g), m.p. 162-165° (from hexane-ethyl acetate), λ_{max} (EtOH) 249 (ϵ 12,600 and 293 (ϵ 11,000) nm; ν_{max} (KBr) 1752, 1700, 1280, and 1240 cm^{-1} ; δ_{H} [$(\text{CD}_3)_2\text{SO}$] 0.90 (6H, d, J 7Hz, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.64-2.25 (3H, m, 2'- CH_2 , CH_2CHMe_2), 3.85 (2H, d, J 7Hz, CH_2CHMe_2), 3.90 (1H, m, 4'-CH), 4.24 (3H, m, 5'- CH_2 , 3'-CH), 5.40 (1H, m, D_2O exchangeable, OH), 6.13 (1H, t, J 6Hz, 1'-CH), 7.81 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.27 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.75 (1H, s, 6-CH), and 11.55 (1H, m, D_2O exchangeable, NH) (Found: C, 44.6; H, 4.65; N, 6.2%). $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_7\text{Br}$ requires C, 44.35; H, 4.9; N, 6.45%).

- 27 -

Examples 18, 19 and 20**0095294**

5-(E-2-Bromovinyl)-5'-O-t-butoxycarbonyl-2'-deoxyuridine
(Example 18), 5-(E-2-Bromovinyl)-3',5'-bis-O-t-butoxycarbonyl-
2'-deoxyuridine (Example 19) and 5-(E-2-Bromovinyl)-3'-O-t-
butoxycarbonyl-2'-deoxyuridine (Example 20).

p-Nitrophenyl t-butyl carbonate (3g) was added to a stirred mixture of 5-(E-2-bromovinyl)-2'-deoxyuridine (2.12g), triethylamine (2.2ml) and 4-dimethylaminopyridine (0.2g) in N,N-dimethylformamide at room temperature. The mixture was stirred at room temperature overnight. It was then partitioned between aqueous hydrochloric acid and ethyl acetate. The organic extract was washed with aqueous sodium carbonate, brine, dried, and evaporated. The residue was chromatographed over silica gel (80g). Elution of the column with ethyl acetate-hexane (3:1) gave two fractions. Fraction A contained a mixture of two compounds. Fraction B afforded 5-(E-2-bromovinyl)-5'-O-t-butoxycarbonyl-2'-deoxyuridine (0.6g); m.p. 170-172° (from ethyl acetate-hexane); λ_{max} (EtOH) 250 (ϵ 14,800) and 293 (ϵ 12,400) nm; ν_{max} (KBr) 1748, 1700, 1470, and 1290 cm^{-1} ; δ_H [(CD₃)₂SO] 1.43 (9H, s, (CH₃)₃C), 2.16 (2H, t, J 6Hz, 2'-CH₂), 3.91 (1H, m, 4'-CH), 4.20 (3H, m, 3'-CH, 5'-CH₂), 5.41 (1H, m, D₂O exchangeable, OH), 6.15 (1H, t, J 6Hz, 1'-CH), 6.84 (1H, d, J 14Hz, CH=CHBr), 7.31 (1H, d, J 14Hz, CH=CHBr), 7.77 (1H, s, 6-CH), and 11.60 (1H, m, D₂O exchangeable, NH) (Found: C, 44.45; H, 4.7; N, 6.4 %. C₁₆H₂₁N₂O₇Br requires C, 44.35; H, 4.9; N, 6.45 %).

Fraction A from above was re-chromatographed over silica gel (50g). Elution of the column with hexane-ethyl acetate (3:2) gave 5-(E-2-bromovinyl)-3',5'-bis-O-t-butoxycarbonyl-2'-deoxyuridine (0.4g); λ_{max} (EtOH) 249 (ϵ 14,200) and 291 (ϵ 12,100) nm; ν_{max} (CHCl₃) 1744, 1710, 1270, and 1150 cm^{-1} ; δ_H (CDCl₃) 150 (9H, s, (CH₃)₃C), 1.54 (9H, s, (CH₃)₃C), 2.08-2.65 (2H, m, 2'-CH₂), 4.30 (3H, m, 4'-CH, 5'-CH₂), 5.11 (1H, m, 3'-CH), 6.40 (1H, dd, J 6Hz, J 8Hz, 1'-CH), 6.67 (1H, d, J 14Hz, CH=CHBr), 7.42 (1H, d, J 14Hz, CH=CHBr), 7.72 (1H, s, 6-CH), and 8.93 (1H, m, D₂O exchangeable, NH) (Found: C, 47.5; H, 5.2; N, 5.1 %. C₂₁H₂₉N₂O₉Br requires C, 47.3; H, 5.5; N, 5.25 %), and 5-(E-2-bromovinyl)-3'-O-t-butoxycarbonyl-

0095294

2'-deoxyuridine (0.23g); λ_{max} (EtOH) 249 (ϵ 13,700) and
292 (ϵ 11,700) nm; ν_{max} (CHCl₃) 1710, 1460, 1270, 1150,
and 1090 cm⁻¹; δ_H (CDCl₃) 1.50 (9H, s, (CH₃)₃C), 2.45
(2H, m, 2'-CH₂), 2.57 (1H, m, D₂O exchangeable, OH), 3.95
(2H, m, 5'-CH₂), 4.17 (1H, m, 4'-CH), 5.20 (1H, m, 3'-CH),
6.26 (1H, t, J 6Hz, 1'-CH), 6.64 (1H, d, J 14Hz, CH=CHBr),
7.33 (1H, d, J 14Hz, CH=CHBr), 7.86 (1H, s, 6-CH), and
9.15 (1H, m, D₂O exchangeable, NH) (Found: C, 44.3;
H, 4.75; N, 6.15 %. C₁₆H₂₁N₂O₇Br requires C, 44.35;
H, 4.9; N, 6.45 %).

0095294

Example 215'-O-Allyloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxyuridine

Allyl chloroformate (0.44ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (1.06g) in pyridine (25ml) at 0° and the mixture was stirred at room temperature for 1 h. The same work-up and chromatography as in Example 14 gave the title compound (0.45g), m.p. 173-175° (from ethyl acetate-hexane), λ_{max} (EtOH) 249 (ϵ 14,500) and 293 (ϵ 12,400) nm; ν_{max} (KBr) 1750, 1710, 1695, 1675, 1285, and 1265 cm^{-1} ; δ_{H} [(CD₃)₂SO] 2.20 (2H, t, J 6.5Hz, 2'-CH₂), 3.95 (1H, m, 4'-CH), 4.26 (3H, m, 5'-CH₂, 3'-CH), 4.59 (2H, m), 5.15-5.47 (2H, m), 5.40 (1H, m, D₂O exchangeable, OH), 5.73-6.05 (1H, m), 6.15 (1H, t, J 6.5Hz, 1'-CH), 6.85 (1H, d, J 14Hz, CH=CHBr), 7.29 (1H, d, J 14Hz, CH=CHBr), 7.77 (1H, s, 6-CH), and 11.60 (1H, m, D₂O exchangeable, NH) (Found: C, 43.65; H, 3.95; N, 6.65 %. C₁₅H₁₇N₂O₇Br requires C, 43.2; H, 4.1; N, 6.7 %).

0095294Example 225'-O-Benzylloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxyuridine

Benzyl chloroformate (1.38ml) was added to a solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (2.14g) in pyridine (40ml) at 0° and the mixture was then stirred at room temperature for 4 h. It was then partitioned between aqueous hydrochloric acid-ethyl acetate. The organic extract was washed with aqueous sodium bicarbonate, dried, and evaporated. The residue was then chromatographed over silica gel (100g). Elution of the column with ethyl acetate-hexane (4:1) gave the title compound (1.0g), m.p. 175-177° (from ethyl acetate-n-hexane); λ_{max} (EtOH) 250 (ε 12,000) and 293 (ε 14,400) nm; ν_{max} (KBr) 1758, 1695, and 1280 cm⁻¹; δ_H [(CD₃)₂SO] 2.19 (2H, t, J 6Hz, 2'-CH₂), 3.96 (1H, m, 4'-CH), 4.30 (3H, m, 3'-CH, 5'-CH₂), 5.17 (2H, s, OCH₂Ph), 6.18 (1H, t, J 6Hz, 1'-CH), 6.89 (1H, d, J 14Hz, CH=CHBr), 7.31 (1H, d, J 14Hz, CH=CHBr), 7.41 (5H, s, ArH), 7.82 (1H, s, 6-CH), and 11.60 (1H, m, D₂O exchangeable, NH) (Found: C, 48.95; H, 4.15; N, 6.15 %. C₁₉H₁₉N₂O₇Br requires C, 48.85; H, 4.1%; N, 6.0 %).

0095294

Example 235-(E-2-Bromovinyl)-5'-O-phenoxy carbonyl-2'-deoxyuridine

Phenyl chloroformate (0.9ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (2g) in pyridine (40ml) at 0° and the mixture was allowed to come to room temperature. It was then stirred at room temperature for 0.5h. The mixture was partitioned between aqueous hydrochloric acid (2M)-ethyl acetate. The organic extract was washed with aqueous sodium bicarbonate, dried and evaporated to give an oil. Chromatography over silica gel (100g) then afforded the title compound (1.8g); λ_{max} (EtOH) 5
249 (ϵ 13,800), and 293 (ϵ 11,500) nm⁻¹; ν_{max} (KBr) 1768, 10
1700, 1282, 1255, and 1212 cm⁻¹; δ_H [(CD₃SO₂)] 2.18 (2H, t, J 6Hz, 2'-CH₂), 4.00 (1H, m, 4'-CH), 4.20-4.50 (3H, m, 10
3'-CH, 5'-CH₂), 5.55 (1H, m, D₂O exchangeable, 3'-OH), 15
6.16 (1H, t, J 6Hz, 1'-CH), 6.86 (1H, d, J 14Hz, CH=CHBr), 7.13-7.50 (6H, m, CH=CHBr, ArH), 7.82 (1H, s, 6-CH), and 20
11.60 (1H, m, D₂O exchangeable, NH) (Found: C, 47.75; H, 3.4; N, 5.95 %. C₁₈H₁₇N₂O₇Br requires C, 47.7; H, 3.8; N, 6.2 %).

Sample 67

0095294

5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(p-nitrophenoxy carbonyl)uridine

p-Nitrophenyl chloroformate (4g) in dichloromethane (10ml) was added to a stirred solution of 5-(E-2-bromovinyl)-2'-deoxyuridine (5.37g) in pyridine (60ml) at 0° and the mixture was stirred at 0° for 1 h. The same work-up and chromatography as in Example 14 gave the title compound (2.2g), m.p. 196-200° (from ethyl acetate), λ_{max} (EtOH) 251 (ϵ 20,900), 259 (ϵ 20,100), and 282 (ϵ 16,500) nm; ν_{max} (KBr) 1775, 1710, 1680, 1525, and 1220 cm^{-1} ; δ_{H} [$(\text{CD}_3)_2\text{SO}$] 2.23 (2H, t, J 6.5Hz, 2'- CH_2), 4.05 (1H, m, 4'-CH), 4.36 (1H, m, 3'-CH), 4.48 (2H, m, 5'- CH_2), 5.50 (1H, m, D_2O exchangeable, OH), 6.20 (1H, t, J 6.5Hz, 1'-CH), 6.86 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.28 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.85 (2H, d, J 9Hz, ArH), 7.83 (1H, s, 6-CH), 8.32 (2H, d, J 9Hz, ArH), and 11.45 (1H, m, D_2O exchangeable, NH) (Found: C, 43.5; H, 3.15; N, 8.25 %. $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_9\text{Br}$ requires C, 43.4; H, 3.25; N, 8.45 %).

Example 25

0095294

5-(E-2-Bromovinyl)-2'-deoxy-5'-O-isopropoxycarbonyluridine

A mixture of 5-(E-2-bromovinyl)-2'-deoxy-5'-O-(p-nitro-phenoxycarbonyl)uridine(0.66g), 4-dimethylaminopyridine (0.5g), and isopropanol (4ml) in pyridine (20ml) was stirred at room temperature for 8 days. The same work-up and chromatography as in Example 14 gave the title compound (0.25g), m.p. 165-168° (from acetone-hexane), λ_{max} (EtOH) 249 (ϵ 14,800) and 293 (ϵ 12,700) nm; ν_{max} (KBr) 1750, 1720, 1695, 1470, 1285, and 1265 cm^{-1} ; δ_{H} [$(\text{CD}_3)_2\text{SO}$] 1.25 (6H, d, J 7.5Hz), 2.20 (2H, t, J 6.5Hz, 2'- CH_2), 3.92 (1H, m, 4'-CH), 4.27 (3H, m, 5'- CH_2 , 3'-CH), 4.77 (1H, m), 5.43 (1H, m, D_2O exchangeable, OH), 6.16 (1H, t, J 6.5Hz, 1'-CH), 6.85 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.32 (1H, d, J 14Hz, $\text{CH}=\text{CHBr}$), 7.77 (1H, s, 6-CH), and 11.60 (1H, m, D_2O exchangeable, NH).

Example 26**0095294**5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(2-hydroxyethoxycarbonyl)-uridine

Ethylene glycol (0.8ml) was added to a stirred mixture
5 of 5-(E-2-bromovinyl)-2'-deoxy-5'-O-(p-nitrophenoxy carbonyl)-uridine (0.36g) in pyridine (5ml) and the mixture was stirred at room temperature for 5 days. The same work-up and chromatography as in Example 14 gave the title compound (0.11g), m.p. 160-168° (from ethanol-ether), λ_{max} (EtOH) 10 249 (ϵ 14,000) and 293 (ϵ 12,300) nm; ν_{max} (KBr) 1750, 1705, 1680, 1470, and 1285 cm^{-1} ; δ_H [(CD₃)₂SO] 2.20 (2H, t, J 6.5Hz, 2'-CH₂), 3.60 (2H, m), 3.80-4.40 (6H, m), 4.84 (1H, m, D₂O exchangeable, OH), 5.45 (1H, m, D₂O exchangeable, OH), 6.16 (1H, t, J 6.5Hz, 1'-CH), 6.88 (1H, d, J 14Hz, 15 CH=CHBr), 7.30 (1H, d, J 6.5Hz, CH=CHBr), 7.80 (1H, s, 6-CH), and 11.60 (1H, m, D₂O exchangeable, NH) (Found: C, 39.7; H, 3.85; N, 6.55 %. C₁₄H₁₇N₂O₈Br requires C, 39.9; H, 4.05; N, 6.65 %).

Example 27**0095294**2'-Deoxy-5'-O-ethoxycarbonyl-5-vinyluridine

To a solution of 2'-deoxy-5-vinyluridine (0.77g, 3.0mmol) in dry pyridine (6ml) at 0° was added ethyl chloroformate (0.41ml, 4.2mmol) and the solution was stirred for 0.5 h at 0°. The solution was partitioned between ethyl acetate and dilute hydrochloric acid and the aqueous layer was again extracted with ethyl acetate. The combined organic extracts were washed with aqueous sodium bicarbonate and dried (magnesium sulphate). On concentration of the ethyl acetate solution crystallisation took place to afford 2'-deoxy-5'-O-ethoxycarbonyl-5-vinyluridine as a white solid (0.53g, 54%), m.p. 145-147°; δ_H [(CD₃)₂SO] 1.24 (3H, t, J 7Hz, CH₃), 2.22 (2H, t, J 6Hz, 5'-H), 3.9-4.4 (6H, m, 3'-H, 4'-H, 5'-H and CH₂CH₃), 5.16 (1H, dd, J 3Hz and 12Hz, CH=CHH (E)), 5.46 (1H, br, D₂O exchangeable, OH), 6.00 (1H, dd, J 3Hz and 18Hz, CH=CHH (Z)), 6.1-6.95 (1H, m, 1'-H and CH=CHH), 7.75 (1H, s, 6-H), and 11.45 (1H, br, D₂O exchangeable, 3-H) (Found: C, 51.55; H, 5.7 N, 8.4 %. C₁₄H₁₈N₂O₇ requires C, 51.55; H, 5.55; N, 8.6 %).

Antiviral Activity**0095294**Method

Vero (African Green Monkey Kidney) cells were grown to confluence in 24 well multidishes, each well being 1.6cm in diameter. The cells were infected with Herpes simplex type 1 virus (HFEM strain) and overlaid with 0.5ml of 0.9% agarose (w/v) in maintenance medium. Test compounds prepared in maintenance medium in concentrations ranging from 100 to 0.03 μ g/ml in half-log dilution steps, were added in 0.5ml volume. The virus infected cultures were then incubated at 37° for 4 days before fixing in 4% formaldehyde solution and staining with carbolfuchsin. The dishes were then examined to find what concentration of test compound caused a 50% reduction in the number of virus plaques formed (PDD_{50} value) and the minimum concentration of test compound which caused cytotoxicity (MTD).

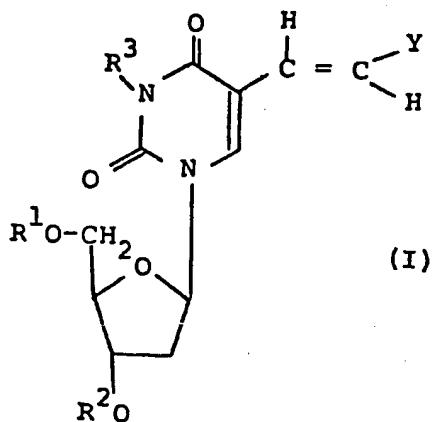
Results**0095294**

<u>Example No.</u>	<u>PDD₅₀</u> <u>µg/ml</u>	<u>µM</u>	<u>MTD (µg/ml)</u>
1	5.3	11.8	>100
2	0.74	1.9	>100
3	1.5	3.8	>100
4	1.1	2.3	>100
5	0.28	0.7	>100
6	0.43	1.1	>100
7	5.0	12.3	>100
8	1.7	3.0	>100
9	1.5	3.0	>100
10	3.3	6.7	>100
11	6.3	12.0	>100
12	12.0	23.0	>100
13	3.8	7.5	>100
14	0.39	0.9	>100
15	0.25	0.6	>100
16	0.44	0.8	100
17	0.22	0.5	>100
18	0.28	0.7	>100
19	2.0	3.8	>100
20	0.18	0.4	>100
21	0.72	1.7	>100
22	0.05	0.1	>100
23	0.18	0.4	>100
24	0.60	1.2	100
25	0.88	2.1	>100
26	0.76	1.8	>100
27	1.5	4.6	>100

0095294

CLAIMS

1. A compound of formula (1):



or a pharmaceutically acceptable salt or ester thereof, in which Y is a hydrogen or halogen atom, and each of R¹, R² and R³ is a hydrogen atom; an acyl radical of the formula X - C - , in which X is a

C₁₋₁₂ alkyl group, an optionally substituted phenyl, or optionally substituted benzyl group, or a carboxy group of the formula HO - C - Z - in which Z is a

branched or straight chain alkylene radical having from 1 to 4 carbon atoms in the chain; an optionally substituted C₁₋₁₂ alkoxy carbonyl group; an optionally substituted C₃₋₁₂ alkenyloxy carbonyl group; an optionally substituted phenoxy carbonyl group; or an optionally substituted phenyl C₁₋₆ alkoxy carbonyl group; provided at least one of R¹, R² and R³ is an optionally substituted alkoxy carbonyl, optionally substituted alkenyloxy carbonyl, optionally substituted phenoxy carbonyl or optionally substituted phenyl C₁₋₆ alkoxy carbonyl group.

- 2 -

0095294

2. A compound according to claim 1, in which R¹, R² or R³ is a C₁₋₆ alkoxy carbonyl group.
3. A compound according to claim 2, in which R¹, R² or R³ is methoxycarbonyl or ethoxycarbonyl.
4. A compound according to claim 1, in which R¹, R² or R³ is an optionally substituted benzyloxycarbonyl group.
5. A compound according to any one of claims 1 to 4, in which X is C₁₋₆ alkyl or Z is (-CH₂-)_n wherein n is 2 or 3.
6. A compound according to claim 1, selected from:
5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-methoxy-carbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3'-O-methoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-methoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-3',5'-bis-O-ethoxycarbonyl-uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3'-O-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-3-ethoxycarbonyluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3,3'-O-bisvaleryluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3'-O-valeryluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyl-3-valeryluridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine
3'-Succinate Sodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine

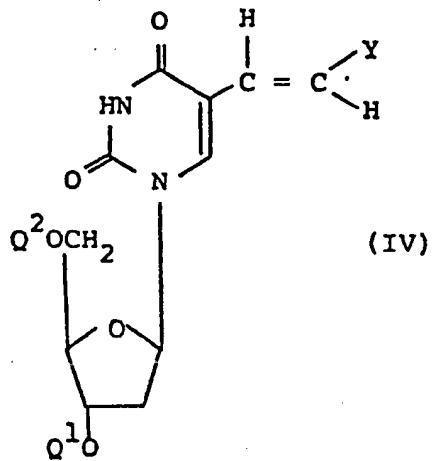
0095294

3'-Phosphate Disodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-ethoxycarbonyluridine
3'-Phosphate Monosodium Salt;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-propoxycarbonyl-
uridine;
5-(E-2-Bromovinyl)-5'-O-n-butoxycarbonyl-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-3',5'-bis-O-butoxycarbonyl-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-5'-O-isobutoxycarbonyl-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-5'-O-t-butoxycarbonyl-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-3',5'-bis-O-t-butoxycarbonyl-2'-
deoxyuridine;
5-(E-2-Bromovinyl)-3'-O-t-butoxycarbonyl-2'-deoxy-
uridine;
5'-O-Allyloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxy-
uridine;
5'-O-Benzylloxycarbonyl-5-(E-2-bromovinyl)-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-5'-O-phenoxy carbonyl-2'-deoxy-
uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(p-nitrophenoxy-
carbonyl)uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-isopropoxycarbonyl-
uridine;
5-(E-2-Bromovinyl)-2'-deoxy-5'-O-(2-hydroxyethoxy-
carbonyl)uridine;
2'-Deoxy-5'-O-ethoxycarbonyl-5-vinyluridine;

- 4 -

0095294

7. A process for preparing a compound of formula (I), which comprises reacting a compound of formula (IV)



wherein Y is as defined in formula (I) and Q¹ and Q² are each hydrogen or O-protecting groups, with an appropriate alkyl, alkenyl, phenyl or phenylalkyl-chloroformate, deprotecting the resultant product if necessary, and optionally thereafter treating the compound of formula (I) thus formed with an acylating agent containing the X - C - group or - Z - C - group,



wherein X and Z are as defined in formula (I).

8. A process according to claim 7, in which Q¹ and Q² are both hydrogen, or one is hydrogen and the other is an O-protecting group.
9. A pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier or excipient.

0095294

- 5 -

10. A compound according to claim 1 for use in the treatment of viral infections.



European Patent
Office

EUROPEAN SEARCH REPORT

0095294

Application number

EP 83 30 2740

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ?)
X, Y	DE-A-3 010 399 (K. GAURI) * Pages 5-7 *	1-10	C 07 H 19/08 A 61 K 31/70
Y	DE-A-2 915 254 (UNIVERSITY OF BIRMINGHAM) * Pages 1-2 *	1-10	
P, D X	EP-A-0 061 283 (BEECHAM) * Pages 1-4; claims *	1-10	
E	EP-A-0 082 668 (BEECHAM) -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl. ?)
			C 07 H 19/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	26-08-1983	VERHULST W.	
CATEGORY OF CITED DOCUMENTS			
X	particularly relevant if taken alone	T : theory or principle underlying the invention	
Y	particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date	
A	technological background	D : document cited in the application	
O	non-written disclosure	L : document cited for other reasons	
P	intermediate document	& : member of the same patent family, corresponding document	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAYSCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.